

Applicant: de Juan, et al
Serial No.: 10/507,461
Filed: September 10, 2004

Examiner: Carter, Kendra D.
Group Art Unit: 1617
Docket No.: SRM0045/US

Title: METHOD FOR SUBRETINAL ADMINISTRATION OF THERAPEUTICS INCLUDING STEROIDS;
METHODS FOR LOCALIZING PHARMACODYNAMIC ACTION AT THE CHOROID AND THE RETINA; AND
RELATED METHODS FOR TREATMENT AND/OR PREVENTION OF RETINAL DISEASES

Remarks

This communication is responsive to the non-final Office Action mailed November 17, 2008. Prior to entry of this paper, claims 1-6, 8, 11, 20, 27, 30, and 58-64 are pending in the application. All claims stand rejected in the non-final Office Action of November 17, 2008.

In this paper, claim 1 has been amended and claim 2 has been canceled. No new matter has been added. Reconsideration of the application in view of the amendments to the claims and the remarks presented below is respectfully requested.

Claim Rejections - 35 U.S.C. §102(b)

Claim 1 stands rejected under 35 U.S.C. §102(b) as being anticipated by Wong et al. (U.S. Pat No. 5,632,984) (Wong '984).

The Office Action states that "Wong 984 teaches intraocular administration of drugs that concentrate the drug at the site of the disease and where biodegradable microcapsules are employed, providing continuous, long-lasting treatment (see abstract and column 3, lines 8-9). The administration is into the posterior segment of the eye allowing diffusion throughout the vitreous within the posterior segment, and further into the entire retina, the choroids and the opposed schlera (i.e., instilling therapeutic medium sub-retinally; see column 4, lines 1-9; addresses claim 1). Administration may be achieved by injection in a saline solution (see column 7, lines 63-65 and column 9, lines 63-67)."

Applicant disagrees with the position taken in the Office Action. Wong '984 relates to the introduction of a drug into the posterior segment of the eye. Introduction into the posterior segment allows diffusion of the drug throughout the vitreous within the posterior segment and further into the entire retina, the choroids and opposed sclera. According to Wong '984 the drug is directly available at the macula, the site where the drug is needed, and will be maintained at the effective dosage (see, col. 4, lines 1-9).

A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference (see, MPEP 2131). The identical invention must be shown in as complete detail as is contained in the

claim. MPEP 2131 citing *Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236, 9 USPQ2d 1913, 1920 (Fed Cir. 1989).

In this paper, claim 1 has been amended in order to clarify that the step of instilling the therapeutic medium sub-retinally comprises injecting a solution including the therapeutic medium directly into the sub-retinal space. Wong '984 fails to describe, either expressly or inherently, a method for administering a therapeutic medium to a posterior segment of an eye comprising instilling a therapeutic medium directly into the sub-retinal space. Rather, Wong '984 is concerned with the introduction of a drug into the posterior segment of the eye into the vitreous where it diffuses throughout the vitreous within the posterior segment and further into the entire retina, the choroids and opposed sclera. The step of instilling the therapeutic medium directly into the sub-retinal space is localizes the action of the therapeutic medium at the choroid and the retina, and minimizes action at other tissues of the eye. Since Wong '984 does not teach or suggest directly instilling a therapeutic medium sub-retinally in order to localize action of the therapeutic medium, Wong '984 does not anticipate claim 1. In view of the foregoing, the rejection of claim 1 under 35 U.S.C. 102(b) as being anticipated by Wong '984 should be withdrawn.

Claim Rejections - 35 U.S.C. §103(a)

Claims 1-4, 6, 7, 8, 11, 20, 27, 58-61, and 63-64 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Wong et al. (U.S. Pat No. 5,869,079) (Wong '079) in view of Wong et al. (U.S. Pat No. 5,632,984) (Wong '984).

Applicant respectfully traverses the rejection of claims 1-4, 6, 7, 8, 11, 20, 27, 58-61, 63 and 64.

The Office Action relies upon a combination of Wong '079 and Wong '984 under 35 U.S.C. §103(a). The determination of obviousness under 35 U.S.C. §103(a) is a legal conclusion based upon factual evidence. See *KSR International Co. v. Teleflex Inc. et al.* 127 S. Ct. 1727 (U.S. 2007). In KSR, the Supreme Court reiterated that determination of obviousness depends upon (1) the scope and content of the prior art; (2) the differences between the prior art and the claims at issue; (3) the level of ordinary skill in the pertinent

art; and (4) an evaluation of any relevant secondary consideration. (See *Graham v. John Deere Co. of Kansas City*, 383 U.S. 1, 17 (1996.))

Therefore, the test for obviousness under 35 U.S.C. §103(a) must take into consideration the invention as a whole. This includes a consideration of the particular problem solved by the elements that define the invention. *Interconnect Planning Corp. v. Feil*, 744 F.2d 1132, 1143, 227 USPQ 543, 551 (Fed. Cir.1985). The Examiner must, as one of the inquiries pertinent to any obviousness inquiry under 35 U.S.C. §103(a), recognize and consider not only the similarities but also the critical differences between the claimed invention and the prior art. *In re Bond*, 910 F.2d 831, 834, 15 USPQ2d 1566 (Fed. Cir. 1990), reh'g denied, 1990 U.S. App. LEXIS 19971 (Fed. Cir.1990).

Moreover, the Examiner must avoid hindsight. M.P.E.P. § 2143.01 (citing *In re Gordon*, 733 F.2d 900, 221 U.S.P.Q. 1125 (Fed. Cir. 1984)). That is, the Examiner cannot use the Applicant's structure as a "template" and simply select elements from the references to reconstruct the claimed invention. *In re Gorman*, 933 F.2d 982, 987, 18 U.S.P.Q.2d (BNA) 1885, 1888 (Fed. Cir. 1991). The fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination. *In re Mills*, 16 USPQ2d 1430 (Fed. Cir. 1990); M.P.E.P. § 2143.01.

The Court in *KSR* reaffirmed that hindsight reasoning is improper and stated that "[a] fact finder should be aware, of course, of the distortion caused by hindsight bias and must be cautious of argument reliant upon ex post reasoning." *KSR Int'l Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 82 USPQ2d at 1397. See also *Graham v. John Deere Co.*, 383 U.S. at 36, 148 USPQ at 474.

The Court of Appeals for the Federal Circuit (CAFC) has also recently revisited the determination of obviousness. In *Ortho-McNeil Pharmaceutical, Inc. v. Mylan Laboratories, Inc. and Mylan Pharmaceuticals, Inc.* the CAFC held that a flexible "teaching-suggestion-motivation" (TSM) test to establish a prima facie case of obviousness remains the primary guarantor against non-statutory hindsight analysis. In accord see *Translogic Tech., Inc.*, 504 F.3d 1249, 1257 (Fed. Cir. 2007). The CAFC, quoting the Supreme Court, stated:

“...a flexible approach to the TSM test prevents hindsight and focuses on evidence before the time of the invention.” *KSR supra*.

The TSM test:

[A]sks not merely what the references disclose, but whether a person of ordinary skill in the art, possessed with the understandings and knowledge reflected in the prior art, and motivated by the general problem facing the inventor, would have been led to make the combination recited in the claims... From this it may be determined whether the overall disclosures, teachings, and suggestions of the prior art, and the level of skill in the art –i.e., the understandings and knowledge of persons having ordinary skill in the art at the time of the invention – support the legal conclusion of obviousness. (See *In re Kahn*, 04-1616, *16 (Fed. Cir. 2006)) (citations omitted).

While *Kahn* was decided before *KSR*, the guidelines set forth there remain appropriate even today.

It is clear that an obviousness analysis still requires a showing of some reason for combining the elements from the prior art in the claimed manner. *Ortho-McNeil supra*; *Takeda Chemical Industries, LTD.*, and *Takeda Pharmaceuticals North America, Inc. v. Alphapharm, Pty., Ltd. and Genpharm, Inc.* 492 F.3d 1350 (Fed. Cir. 2007). This showing must not be a general showing. Rather, it must be one that would have suggested making the specific modifications needed to achieve the claimed invention. See *Takeda*. See also *In re Jones*, 958 F.2d 347 (Fed. Cir. 1992); *Dillon*, 919 F.2d 688; *Grabiak*, 769 F.2d 729; *In re Lalu*, 747 F.2d 703 (Fed. Cir. 1984).

When these guidelines are applied to the present rejection, it is clear that there is no motivation to combine the teachings of Wong ‘079 and Wong ‘984, and that this rejection under 35 U.S.C. §103(a) is made using impermissible hindsight.

Wong ‘984 relates to the treatment of macular degeneration by the administration of drugs into the posterior segment of the eye to provide a therapeutically effective amount of the drug. Introduction into the posterior segment allows diffusion of the drug throughout the vitreous within the posterior segment and further into the entire retina, the

choroids and opposed sclera. Of particular interest is the administration of interferon, particularly α -2a-interferon. In some embodiments the drug is delivered in biocompatible, biodegradable microcapsules in order to provide a slow release. As described in Wong '984, the introduction of the drug into the posterior segment allows diffusion of the drug throughout the vitreous within the posterior segment and further into the entire retina, the choroids, and opposed sclera. According to Wong '984 the drug is directly available at the macula, the site where the drug is needed, and will be maintained at an effective dosage (see, col. 4, lines 1-9).

Wong '079 relates to the use of solid slow release biodegradable implants. Wong '079 teaches that the release of the drug can be controlled by the rate of transport through the polymeric matrix of the implant and by the addition of a release modulator to the implant. The release modulator may act to accelerate or retard the rate of release. The implants of Wong '079 are of dimensions commensurate with the size and shape of the region selected as the site of implantation and will not migrate from the insertion site following implantation. The implants will also preferably be at least somewhat flexible so as to facilitate both insertion of the implant at the target site and accommodation of the implant. Wong '079 teaches that suitable sites include the anterior chamber, posterior chamber, vitreous cavity, suprachoroidal space, subconjunctiva, episcleral, intracorneal, epicorneal and sclera.

With respect to claims 1 and 20, Wong '079 is concerned with the implantation of solid biodegradable implants. Wong '079 does not teach or suggest instilling a therapeutic medium sub-retinally; wherein the step of instilling comprises directly injecting a solution including the therapeutic medium directly into the sub-retinal space. The act of instilling a bioactive agent directly into the sub-retinal space localizes the action of the therapeutic medium at the choroid thereby minimizing action at other tissues of the eye. The Office Action states at page 15 that

Wong '984 is used as a reference to teach that therapeutic mediums such as those taught by Wong '079 can be administered via intraocular injection with a saline solution. Wong '079 provides the teaching that the therapeutic medium can be administered sub-retinally. The motivation to

combine Wong '984 and Wong '079 references is because both teach intraocular administration with biodegradable microcapsules. Thus, the biodegradable microcapsules of Wong '079 can be administered in a saline solution because Wong '984 teaches that it is known in the art for biodegradable microcapsules to be administered by injection in a saline solution (see abstract, column 3, lines 8-9; column 7, lines 63-65 and column 9, lines 63-67).

Wong '984 and Wong '079 operate in quite different ways using different types of materials and methods. Wong '984 is practiced with a liquid that is injected into the posterior segment of the eye and diffuses to the site of treatment. By contrast, Wong '079 is practiced with a solid implant that is implanted at a specific site and is intended to be non-migratory once positioned. The Office Action states that "Wong '984 is used as a reference to teach that therapeutic mediums such as those taught by Wong '079 can be administered via intraocular injection with a saline solution." Applicant does not agree. Microparticles are administered via a saline solution in order to deliver a large number of particles which diffuse to the treatment site. By contrast, the implants of Wong '079 are designed to be implanted at a target site where they remain stationary. The implants of Wong '079 are dimensioned commensurate with the size and shape of the implantation site. The implants of Wong '079 are not designed for delivery via a saline solution. Rather, a single implant is implanted directly at the desired treatment site where it remains throughout the course of treatment. There is no motivation to combine Wong '079 and Wong '984 because to do so would be in direct contradiction to the teachings of Wong '079, including the advantages of utilizing a solid stationary implant comprising a hydrophilic and hydrophobic entity to control elution rate; and the further ability to control the elution rate of release, period of treatment, and drug concentration by varying the size and form of the implant. The combination of Wong '079 and Wong '984 has been made using impermissible hindsight analysis. Due to the substantial differences in the two references as discussed above, there would be no motivation to combine the references as suggest in the Office Action. The proposed combination of Wong '984 and Wong '079 cannot render the present invention obvious under 35 U.S.C. §103(a) unless the Examiner has used impermissible non-statutory hindsight analysis.

Claim 58 relates to a method for administering a therapeutic medium to a posterior segment of an eye. The method comprises the step of: implanting a sustained release delivery device in a sub-retinal space; wherein said sustained release delivery device comprises: (a) a core comprising a biocompatible matrix and the therapeutic medium; and (b) a jacket surrounding the core comprising a biocompatible membrane comprising a polymer selected from polyacrylates, polyvinylidenes, polyvinyl chloride copolymers, polyurethanes, polystyrenes, polyamides, cellulose acetates, cellulose nitrates, polysulfones, polyphosphazenes, polyacrylonitriles, poly(acrylonitrile/covinyl chloride), derivatives, copolymers, and mixtures thereof.

Neither Wong '079 nor Wong '984 teach or suggest a method of treating an eye comprising implanting a sustained release delivery device comprising a core comprising a biocompatible polymer and a therapeutic medium; and a jacket surrounding said core comprising a biocompatible membrane comprising a polymer selected from polyacrylates, polyvinylidenes, polyvinyl chloride copolymers, polyurethanes, polystyrenes, polyamides, cellulose acetates, cellulose nitrates, polysulfones, polyphosphazenes, polyacrylonitriles, poly(acrylonitrile/covinyl chloride), derivatives, copolymers, and mixtures thereof. The surrounding jacket allows the elution rate of the therapeutic medium to be controlled, for example, by selection of the polymer type and/or thickness.

With respect to claims 58-61 and 63-64, it is admitted in the Office Action that "Wong et al. does not specifically teach the polymers polyacrylates, polyvinylidenes, polyvinyl chloride copolymers, polyurethanes, polystyrenes, polyamides, cellulose acetates, cellulose nitrates, polysulfones, polyphosphazenes, polyacrylonitriles, poly(acrylonitrile/covinyl chloride), derivatives, copolymers, and mixtures thereof." However, the Office Action goes on to conclude that ... "To one of ordinary skill in the art at the time of the invention would have found it obvious and motivated to combine the method of Wong et al. and the specific polymers disclosed in claim 58 because of the following teachings of Wong et al.: 1) the selection of the polymeric composition employed will vary with the site of administration, the desired period of treatment, patient tolerance, the nature of the disease to be treated and the like (see column 5, lines

27-33); 2) characteristics of the polymers will include biodegradability at the site of implantation, compatibility with the agent of interest, ease of encapsulation and the half-life in the physiological environment (see column 5, lines 27-33); and 3) biodegradable polymeric compositions may be organic esters, ethers, anhydrides, amides, orthoesters, or the like (see column 5, lines 38-53).”

Applicant does not agree with the position taken in the Office Action. As discussed hereinabove, there must be some suggestion to make the specific modifications needed to achieve the claimed invention. The general guidelines provided in Wong ‘079 for desirable characteristics would in no way teach or suggest the use of Applicant’s specifically claimed implants having the structure as set forth in claim 58 including a core comprising a biocompatible polymer and a therapeutic medium; and a jacket surrounding said core comprising a biocompatible membrane comprising a polymer selected from polyacrylates, polyvinylidenes, polyvinyl chloride copolymers, polyurethanes, polystyrenes, polyamides, cellulose acetates, cellulose nitrates, polysulfones, polyphosphazenes, polyacrylonitriles, poly(acrylonitrile/covinyl chloride), derivatives, copolymers, and mixtures thereof. The implants of Wong ‘079 may be monolithic implants (i.e., having the active agent homogeneously distributed through the polymeric matrix) or encapsulated implants (i.e., where a reservoir of active agent is encapsulated by the polymeric matrix). Wong ‘079 does not teach or suggest the use of an implant wherein the core comprises a biocompatible polymer and a therapeutic medium. Rather, Wong ‘079 specifically teaches a system for modulating release of drug wherein the rate of release is controlled by the rate of transport through the polymeric matrix and the action of the modulator. The disclosed polymers and modulators act together to define the rate of release from the implant. There is no reason to modify the polymeric system in Wong’079 to the polymer systems defined in Applicant’s invention since to do so would be expected to change the rate of release from the implant and the ability to control the rate of release with the use of modulators. Wong ‘984 does not cure the deficiencies in Wong ‘079 with respect to the claimed polymer systems. Due to the differences in the two references it is respectfully submitted that the combination of Wong ‘984 and Wong ‘079 cannot render the present invention obvious under 35 U.S.C. §103(a) unless the

Applicant: de Juan, et al
Serial No.: 10/507,461
Filed: September 10, 2004

Examiner: Carter, Kendra D.
Group Art Unit: 1617
Docket No.: SRM0045/US

Title: METHOD FOR SUBRETINAL ADMINISTRATION OF THERAPEUTICS INCLUDING STEROIDS;
METHODS FOR LOCALIZING PHARMACODYNAMIC ACTION AT THE CHOROID AND THE RETINA; AND
RELATED METHODS FOR TREATMENT AND/OR PREVENTION OF RETINAL DISEASES

Examiner has used impermissible non-statutory hindsight analysis. In view of the foregoing, it is submitted that the rejection over Wong '079 in view of Wong '984 has been overcome and should be withdrawn.

In view of the foregoing, the rejection of claims 1, 3-4, 6, 7, 8, 11, 20, 27, 58-61, and 63-64 under 35 U.S.C. §103(a) as being unpatentable over Wong '079 in view of Wong '984 has been overcome and should be withdrawn.

Claims 5, 19, and 62 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Wong et al. (U.S. Pat No. 5,869,079) (Wong '079) in view of Wong et al. (U.S. Pat No. 5,632,984) (Wong '984) as applied to claims 1-4, 6, 7, 8, 11, 20, 27, 58-61, 63 and 64 above, and further in view of Hughes et al. (U.S. Pat No. 5,962,027) (Hughes '027).

Applicant respectfully traverses the rejection of claims 5, 19, and 62 under 35 U.S.C. §103(a).

Claim 5 is a dependent claim that includes all of the limitations of the independent claim 1. Claim 1 is patentable for the reasons set forth herein. Therefore, claim 5 is also patentable for at least the same reasons as presented for independent claim 1.

Claim 62 is a dependent claim that includes all of the limitations of the independent claim 58. Claim 58 is patentable for the reasons set forth herein. Therefore, claim 62 is also patentable for at least the same reasons as presented for independent claim 58.

Claim 19 has been cancelled.

Claims 1, 8, and 11 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Louis (U.S. Patent No. 5,641,750) (Louis) in view of Wong et al. (U.S. Patent No. 5,869,079) (Wong '079), and further view of Hughes et al. (U.S. Patent No. 5,962,027) (Hughes).

Applicant respectfully traverses the rejection of claims 1, 8, and 11 under 35 U.S.C. §103(a).

In this paper, claim 1 has been amended in order to clarify that the step of instilling the therapeutic medium sub-retinally comprises injecting a solution including the therapeutic medium directly into the sub-retinal space.

Louis relates to a method for treating vision loss due to photoreceptor degeneration by administering a therapeutically effective amount of glial cell line-derived neurotrophic factor (GDNF) protein product. According to one aspect of the invention, methods are provided for treating vision loss due to photoreceptor degeneration by administering a therapeutically effective amount of GDNF protein product. It is contemplated that such GDNF protein products would include a GDNF protein such as that depicted by the amino acid sequence set forth in SEQ ID NO:1, as well as variants and derivatives thereof. It is reported that administration of GDNF protein product promotes the survival and regeneration of damaged photoreceptor neurons, which are the main population of neurons damaged in retinal degenerations leading to blindness.

According to Louis, GDNF protein product may be administered intraocularly at a dose between about 0.001 mg/day and 10 mg/day, preferably at a dose between about 0.01 mg/day and 1 mg/day, and most preferably at a dose between about 0.1 mg/day and 0.5 mg/day. It is reported that the delivery means for the administration of a GDNF protein product in the treatment of ophthalmic conditions or diseases may involve topical formulations, ocular inserts, ocular injection, ocular implants, cell therapy or gene therapy.

As admitted in the Office Action, Louis does not teach administration to the posterior segment of the eye by directly instilling a solution therapeutic medium sub-retinally. The Office Action relies upon Wong '079 and Hughes to cure the deficiency in Louis under 35 U.S.C. §103(a).

The determination of obviousness under 35 U.S.C. §103(a) is a legal conclusion based upon factual evidence. *KSR International Co. v. Teleflex Inc. et al.* 127 S. Ct. 1727 (U.S. 2007). In KSR, the Supreme Court reiterated that determination of obviousness depends upon (1) the scope and content of the prior art; (2) the differences between the prior art and the claims at issue; (3) the level of ordinary skill in the pertinent art; and (4) an evaluation of any relevant secondary consideration. *Graham v. John Deere Co. of Kansas City*, 383 U.S. 1, 17 (1996.)

Therefore, the test for obviousness under 35 U.S.C. §103(a) must take into consideration the invention as a whole. This includes a consideration of the particular

Applicant: de Juan, et al
Serial No.: 10/507,461
Filed: September 10, 2004

Examiner: Carter, Kendra D.
Group Art Unit: 1617
Docket No.: SRM0045/US

Title: METHOD FOR SUBRETINAL ADMINISTRATION OF THERAPEUTICS INCLUDING STEROIDS;
METHODS FOR LOCALIZING PHARMACODYNAMIC ACTION AT THE CHOROID AND THE RETINA; AND
RELATED METHODS FOR TREATMENT AND/OR PREVENTION OF RETINAL DISEASES

problem solved by the elements that define the invention. *Interconnect Planning Corp. v. Feil*, 744 F.2d 1132, 1143, 227 USPQ 543, 551 (Fed. Cir.1985). The Examiner must, as one of the inquiries pertinent to any obviousness inquiry under 35 U.S.C. §103, recognize and consider not only the similarities but also the critical differences between the claimed invention and the prior art. *In re Bond*, 910 F.2d 831, 834, 15 USPQ2d 1566 (Fed. Cir. 1990), *reh'g denied*, 1990 U.S. App. LEXIS 19971 (Fed. Cir.1990).

Moreover, the Examiner must avoid hindsight. M.P.E.P. § 2143.01 (citing *In re Gordon*, 733 F.2d 900, 221 U.S.P.Q. 1125 (Fed. Cir. 1984)). That is, the Examiner cannot use the Applicant's structure as a "template" and simply select elements from the references to reconstruct the claimed invention. *In re Gorman*, 933 F.2d 982, 987, 18 U.S.P.Q.2d (BNA) 1885, 1888 (Fed. Cir. 1991). The fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination. *In re Mills*, 16 USPQ2d 1430 (Fed. Cir. 1990); M.P.E.P. § 2143.01.

The Court in *KSR* reaffirmed that hindsight reasoning is improper and stated that "[a] fact finder should be aware, of course, of the distortion caused by hindsight bias and must be cautious of argument reliant upon ex post reasoning." *KSR Int'l Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 82 USPQ2d at 1397. See also *Graham v. John Deere Co.*, 383 U.S. at 36, 148 USPQ at 474.

The Court of Appeals for the Federal Circuit (CAFC) has also recently revisited the determination of obviousness. In *Ortho-McNeil Pharmaceutical, Inc. v. Mylan Laboratories, Inc.* and *Mylan Pharmaceuticals, Inc.* the CAFC held that a flexible "teaching-suggestion-motivation" (TSM) test to establish a prima facie case of obviousness remains the primary guarantor against non-statutory hindsight analysis. In accord see *Translogic Tech., Inc.*, 504 F.3d 1249, 1257 (Fed. Cir. 2007). The CAFC, quoting the Supreme Court, stated:

"...a flexible approach to the TSM test prevents hindsight and focuses on evidence before the time of the invention." *KSR supra*.

The TSM test:

[A]sks not merely what the references disclose, but whether a person of ordinary skill in the art, possessed with the understandings and knowledge reflected in the prior art, and motivated by the general problem facing the inventor, would have been led to make the combination recited in the claims... From this it may be determined whether the overall disclosures, teachings, and suggestions of the prior art, and the level of skill in the art –i.e., the understandings and knowledge of persons having ordinary skill in the art at the time of the invention – support the legal conclusion of obviousness. (*In re Kahn*, 04-1616, *16 (Fed. Cir. 2006)) (citations omitted).

While *Kahn* was decided before *KSR*, the guidelines set forth there remain appropriate even today.

It is clear that an obviousness analysis still requires a showing of some reason for combining the elements from the prior art in the claimed manner. *Ortho-McNeil supra*; *Takeda Chemical Industries, LTD.*, and *Takeda Pharmaceuticals North America, Inc. v. Alphapharm, Pty., Ltd. and Genpharm, Inc.* 492 F.3d 1350 (Fed. Cir. 2007). This showing must not be a general showing. Rather, it must be one that would have suggested making the specific modifications needed to achieve the claimed invention. See *Takeda*. See also *In re Jones*, 958 F.2d 347 (Fed. Cir. 1992); *Dillon*, 919 F.2d 688; *Grabiak*, 769 F.2d 729; *In re Lalu*, 747 F.2d 703 (Fed. Cir. 1984).

When these guidelines are applied to the present rejection, it is clear that there is no motivation to combine the teachings of *Louis* with *Wong '079* or *Hughes*, and that the rejection is made using impermissible hindsight.

Louis relates to a method for treating vision loss due to photoreceptor degeneration by administering a therapeutically effective amount of glial cell line-derived neurotrophic factor (GDNF) protein product. According to one aspect of the invention, methods are provided for treating vision loss due to photoreceptor degeneration by administering a therapeutically effective amount of GDNF protein product. It is reported that administration of GDNF protein product promotes the survival and regeneration of damaged photoreceptor neurons, which are the main population of neurons damaged in retinal degenerations leading to blindness. *Louis* specifically teaches that the delivery

methods includes topical formulations, ocular inserts, ocular injection, ocular implants, cell therapy or gene therapy. As admitted in the Office Action, Louis does not teach administration to the posterior segment of the eye by instilling a solution comprising a therapeutic medium sub-retinally.

Louis reports a number of different delivery methods, but does not teach or suggest direct sub-retinal instillation. Here, there is no motivation to modify the teachings of Louis using either Wong '079 or Hughes. Wong '079 relates to compositions and methods for biodegradable implants that are formulated to provide a controlled, sustained drug release. The release rate is modulated by combining in the implant hydrophobic and hydrophilic agents. Hughes relates to a method for the preparation of a graft for transplantation into the subretinal area of a host eye. Louis describes precise delivery methods that are suitable for treating photoreceptor degeneration, which do not include sub-retinal instillation.

There is no motivation to modify the specifically identified treatment methods by combining Louis with either Wong '079 or Hughes. Specifically, there is no reason to modify Louis, at least in part, because Louis specifically reports the suitable delivery methods, and there is no reasonable expectation that photoreceptor degeneration can be treated by GDNF protein using subretinal instillation. Additionally, both Wong '079 and Hughes relate to the implantation of solid implants or grafts into the eye. There is no motivation to modify Louis because there is no reason to conclude that direct liquid instillation will function like a solid implant or graft when sub-retinally implanted. The Office Action has combined Louis with Wong '079 or Hughes simply because these references relate to sub-retinal implantation. Here, the Examiner has attempted to assemble the elements of Applicant's claims from the prior art using Applicant's claims as roadmap, without motivation for making the proposed combination or reasonable expectation of success in making the proposed combination.

In view of the foregoing, the rejection of claims 1, 8, and 11 under 35 U.S.C. §103(a) as being unpatentable over Louis in view of Wong '079 and further view of Hughes et al. has been overcome and should be withdrawn.

Applicant: de Juan, et al
Serial No.: 10/507,461
Filed: September 10, 2004

Examiner: Carter, Kendra D.
Group Art Unit: 1617
Docket No.: SRM0045/US

Title: METHOD FOR SUBRETINAL ADMINISTRATION OF THERAPEUTICS INCLUDING STEROIDS;
METHODS FOR LOCALIZING PHARMACODYNAMIC ACTION AT THE CHOROID AND THE RETINA; AND
RELATED METHODS FOR TREATMENT AND/OR PREVENTION OF RETINAL DISEASES

CONCLUSION

It is respectfully submitted that the claims and the present application are now in condition for allowance. Approval of the application and allowance of the claims is earnestly solicited. In the event that a phone conference between the Examiner and the undersigned would help resolve any issues in the application, the Examiner is invited to contact undersigned at (651) 275-9830.

Dated: May 18, 2009

Respectfully Submitted,

By: 

Scott R. Pribnow, 43,869
Customer No. 72870
Phone: 651-275-9830
Facsimile: 651-351-2954

SRP/jj/53115